Discovery contributes to future treatment of cervical cancer

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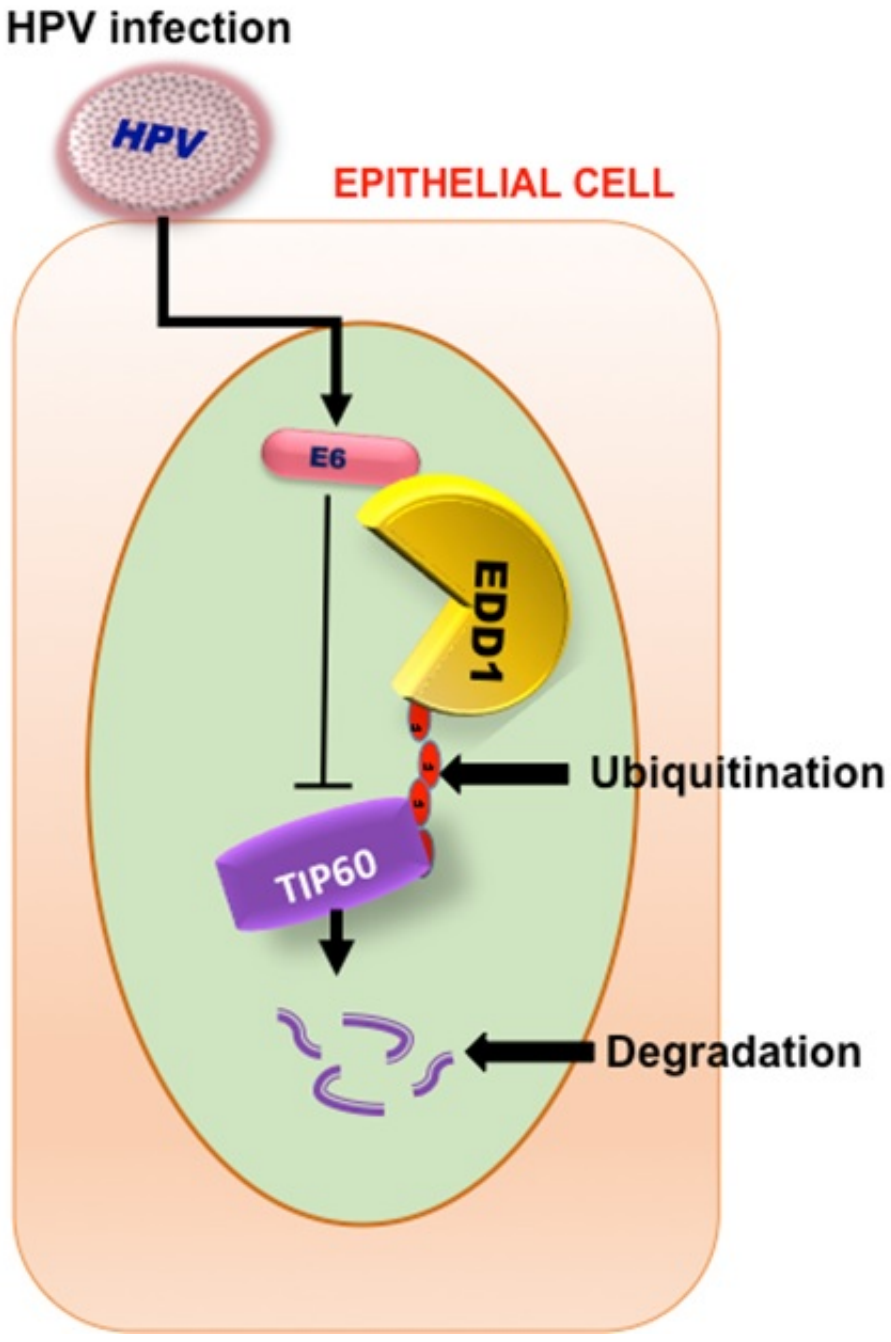

The molecular mechanism for the action of HPV E6, the HPV oncogene, on proteins EDD1 and TIP60. HPV E6 binds with EDD1 to ubiquitinate TIP60, leading to the degradation of TIP60, eventually resulting in tumor tumorigenesis. Credit: National University of Singapore

A team of scientists from Cancer Science Institute of Singapore (CSI Singapore) at the National University of Singapore (NUS) has uncovered new molecular interactions involved in the development of cervical cancer. Proteins EDD1 and TIP60 were found to interact with the Human Papilloma Virus (HPV), which causes cervical cancer in humans. EDD1 is an E3 ubiquitin ligase involved in degrading cellular proteins, while TIP60 act as a tumor suppressor protein, and can both be found in the human body.

The research team, comprising Assistant Professor Sudhakar Jha, Dr Vanitha K. Subbaiah and Mr Zhang Yanzhou, found that HPV E6 oncogene interacts with EDD1 to destabilise the TIP60 protein, thereby resulting in an increased tumorigenesis. In support of this finding, experiments also revealed that an increase in cellular TIP60 levels could inhibit cancer cell growth.

The findings of the study were first published online in the journal *Oncogene* on 3 August 2015.

Previous studies have implicated the roles of both EDD1 and TIP60 in cancer progression, however their roles in viral-mediated cancers have not been well-explored. Notably, this study is one the few which explores the functional role of TIP60 in viral-mediated cancers. It is also the first to suggest EDD1 as a novel interacting partner of TIP60, a

finding which advances the understanding of how this pathway could contribute to cancer progression not only in cervical cancer, but also in many other cancer types such as breast and ovarian cancer.

Oncoviruses (cancer-causing viruses) are said to account for about 12% of new cancer cases annually. Cervical cancer, which is the cancer of the cervix, accounts for about 8% of all cancer cases worldwide and is the fourth most common cause of cancer and deaths from cancer in women. Infections with cancer-causing viruses such as HPV are a major health burden worldwide, and contribute significantly to patient mortality. Availability of prophylactic vaccines hold promises in the prevention of the disease, but unfortunately does not help already-infected patients.

Said Asst Prof Jha, "We are excited about this discovery. Understanding how the two proteins interact with HPV E6 oncogene is a critical first step towards developing methods to target HPV-induced cancers as there is no specific treatment available at the moment. Our team is currently developing methods that can be used to screen small molecule inhibitors of EDD1 and also looking into how the regulation of TIP60 levels can be translated into therapeutic advances for the treatment of viral-mediated cancers such as cervical cancer. If successful, this could potentially be a significant breakthrough."

More information: V K Subbaiah et al. E3 ligase EDD1/UBR5 is utilized by the HPV E6 oncogene to destabilize tumor suppressor TIP60, *Oncogene* (2015). DOI: 10.1038/onc.2015.268

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